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The Toxicity of Some Related Halogenated Derivatives of Phenol

By E. F. Stohlman*

As a result of preliminary field trials to determine the molluscacidal activity of 10 organic compounds previously laboratory tested, Nolan and Berry (*1*) reported pentabromophenol and sodium pentachlorophenate showed promising molluscacidal activity. As this work was extended and additional field tests were made, Berry et al. (*2*) subsequently reported the marked molluscacidal effectiveness of the same compounds and of four others against *Australorbis glabratus* in endemic areas of schistosomiasis in Puerto Rico. These compounds served as the basis for the toxicity studies reported here.

Experimental Procedures

The compounds, pentachlorophenol, the copper salt of pentachlorophenol, pentabromophenol, 2,4,6-tribromophenol, the sodium salt of 2,4,6-triiodophenol, 2,4,6-triiodophenol, and Santobrite [1] used in this work were supplied by the Laboratory of Tropical Diseases of the National Institutes of Health. They were samples of the same lots of the respective compounds employed in the previous work (*1*, *2*).

The solutions were made up daily. The water soluble sodium derivatives were obtained by adding the theoretical amount of sodium hydroxide to each compound, except the sodium salt of 2,4,6-triiodophenol which was used directly. The copper salt of pentachlorophenol was administered as a suspension in Tween 20 because of its insolubility in water. Santobrite was readily water soluble and was administered as an aqueous solution. The compounds were administered by stomach tube to growing female rats. For the most part, all doses were administered in the same volume of 10 cc. per kilo. Dosages have been expressed in terms of the active ingredient present in the

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[1] Registered trade name for Monsanto's sodium pentachlorophenate, labeled; sodium pentachlorophenate 79 percent; sodium salts of other chlorophenols 11 percent; inert ingredients 10 percent. The trade names are carried as a means of identifying the products under discussion and do not represent endorsement of the products by the Public Health Service.

samples, except those of Santobrite which have been expressed as such.

In the acute toxicity experiments, a single administration was given, whereas in the subacute toxicity, five successive daily administrations were given except where otherwise indicated. The animals were kept in metabolism cages and fed ground Purina Chow Pellets [2] and water ad libitum. Animals were observed for about 1 week preceding, and a minimum of 11 days following, administration of the drug. The animals were weighed immediately preceding, and daily during, the course of administrations; otherwise, at 3–5 day intervals. A record of the amount of food consumed was maintained. Autopsies were regularly performed on animals dying during the course of the study and on all survivors at the end of the observational period. No attempt was made to note other than gross changes, and no examination was made of brain and spinal cord.

Results

Acute Toxicity

The results are shown in table 1. The LD_{50} was determined only in the case of Santobrite and was 100 mg. per kilo. The approximate LD_{50} in mg. per kilo of pentachlorophenol was between 125 and 200; the copper salt of pentachlorophenol, about 600; pentabromophenol, slightly more than 200; 2,4,6-tribromophenol, less than 2,000; the sodium salt of 2,4,6-triiodophenol, more than 2,500; and 2,4,6-triiodophenol, less than 2,500.

The consistency with which symptoms were produced, the degree of their intensity, and the rapidity of their onset in all animals receiving identical doses of a given compound indicated relatively rapid and uniform absorption of all compounds from the gastrointestinal tract, except the copper salt of pentachlorophenol. With this compound there was a lack of uniformity of symptoms produced and a relatively wide range in dosage producing equivalent lethal effects.

In general, the symptoms produced by all the compounds, except pentabromophenol, were characteristic of those produced by pentachlorophenol and consisted of an increased respiratory rate and amplitude, followed by loss of muscle tone, collapse, and death in animals sufficiently poisoned. The symptoms from pentabromophenol were increased respiratory rate and amplitude, with general body tremors, occasional convulsions, and death in animals sufficiently poisoned. With certain differences, they simulated those of DDT poisoning in the rat *(3)*; the whole syndrome appeared to be a more rapid version of DDT poisoning. The onset of symptoms was a matter of a few minutes compared to 4–6 hours with DDT. Depending upon their severity, their duration was a few minutes to about 3 hours, ending in

[2] A commercial product said to provide all the essential elements necessary for normal growth and development of rats.

Table 1. *Acute toxicity of certain halogenated derivatives of phenol in rats,*[1] *by oral administration*

Series	Dose gm/kg	Diluent	Number dead/ number used	Remarks
		Pentachlorophenol as a sodium salt		
(2)	0.200	2 percent solution in distilled water.	10/10	Labored respiration, depression and death in 50 minutes–8 hours.
	.125	25 percent solution in distilled water.	0/10	Transitory labored respiration and depression.
		Pentachlorophenol as a copper salt		
(3)	1.000	20 percent suspension in Tween 20.	10/10	Increased respiratory rate with severe depression and death in ½–15 hours.
	.650	20 percent suspension in Tween 20.	4/10	Same with death in 3–14 hours.
	.400	8 percent suspension in Tween 20.	4/10	Same with death in 4½–15 hours.
	.200	2 percent suspension in Tween 20.	0/10	Moderately increased respiratory rate and depression. Recovered in 10 hours.
		Pentabromophenol as a sodium salt		
(4)	0.300	3 percent solution in distilled water.	9/10	Labored respiration, salivation, depression and death in 2–15 hours.
	.200	2 percent solution in distilled water.	4/10	Do.
	.150	3 percent solution in distilled water.	0/10	Labored respiration and mild depression. Recovered in 10 hours.
		Santobrite		
(5)	0.150	1.5 percent solution in distilled water.	9/10	Increased respiratory rate, depression and death in ¾–6 hours.
	.100	1 percent solution in distilled water.	5/10	Do.
	.050	0.5 percent solution in distilled water.	0/10	Increased respiratory rate and mild depression. Recovered in 6 hours.
		2,4,6-Tribromophenol as a sodium salt		
(6)	2.500	25 percent solution in distilled water.	10/10	Severe general tremors. Occasional convulsions. Death in 10–20 minutes.
	2.000	20 percent solution in distilled water.	10/17	Severe general tremors. Died in ½–1¼ hours.
	1.000	----do----	3/20	Do.
		2,4,6-Triiodophenol as a sodium salt [7]		
(7)	4.000	40 percent in distilled water----	10/10	Labored respiration and depression. Died in 1½–15 hours.
	2.500	----do----	6/20	Do.
	1.500	30 percent in distilled water----	0/20	Increased respiratory rate and depression.
		2,4,6-Triiodophenol as a sodium salt		
(8)	3.500	35 percent in distilled water----	7/10	Labored respiration, depression and death in ½–1 hour.
	2.500	25 percent in distilled water----	5/20	Labored respiration, depression and death in 1–8 hours.
	1.500	15 percent in distilled water----	0/18	Labored respiration and depression

[1] Initial weights 63–155 gm.
[2] Mild to severe hemorrhagic congestion in the lungs.
[3] Mild to moderate congestion in the lungs with petechial hemorrhages. In this series 5 cc. per kilo olive oil was administered just preceding administration of the pentachlorophenol.
[4] Mild to moderate congestion in the lungs with a few petechial hemorrhages.
[5] Mild to severe hemorrhagic congestion in the lungs.
[6] Congested lungs.
[7] Supplied as the salt.
[8] Mild to severe congestion and hemorrhages in the lungs.

death or rather rapid recovery. However, although the severity of the general body tremors appeared to be of about the same order as those produced by comparable DDT poisoning, the convulsive seizures appeared to be fewer in number and somewhat less severe.

In table 2 are data on the weight changes in survivors of the acute toxicity experiments. Some weight loss occurred during the first day following a single administration of an approximate LD_{50} dose of each of the foregoing compounds, except the copper salt of pentachlorophenol in which a gain in weight occurred. Substantial gains in weight were shown by survivors in all groups during the 2 to 3 weeks following administration of a single dose.

Gross Post-Mortem Findings

Most apparent of the pathologic changes produced were in the lungs. These covered a range of mild to severe congestion and frequent petechial hemorrhages. All the compounds had the common characteristic of producing these effects in the lungs in varying degrees, somewhat proportional to the size of the dose administered. In addition, the large doses of 2,4,6-triiodophenol produced severe inflammation of the mucous membrane of the pylorus and fundus of the stomach with corrosion and hemorrhages. These were also produced by the larger doses of 2,4,6-tribromophenol but to a considerably lesser degree in severity. The smaller doses of these compounds produced only moderate inflammation of the mucosa of the stomach and intestines. Effects of the other compounds on the stomach were mild to moderate congestion of the mucosa.

Subacute Toxicity

From the data presented in table 3 the LD_{50} of Santobrite was 100 mg. per kilo, and the approximate LD_{50} of pentachlorophenol was slightly less than 150; the copper salt of pentachlorophenol, about 400; pentabromophenol, more than 250; 2,4,6-tribromophenol, less than 1,000; the sodium salt of 2,4,6-triiodophenol, less than 1,500; and 2,4,6-triiodophenol, less than 1,500.

The LD_{50} of Santobrite and the approximate LD_{50} of pentachlorophenol and pentabromophenol, when given once daily for five consecutive doses, were essentially the same as that obtained from the administration of a single dose. This is good evidence that these compounds do not produce a cumulative toxicity on repeated administration. This conclusion is also indicated by the weight changes in rats receiving five daily doses. On the maximum tolerated dose, gains in weight were obtained both during and following drug administration. The survivors of higher doses lost weight during administration but after the drugs were discontinued gained rapidly.

Evidence of some cumulative toxicity was obtained with 2,4,6-tri-

bromophenol, 2,4,6-triiodophenol, and the copper salt of pentachlorophenol. An increase of one to threefold in the LD_{50} was obtained from five daily doses of these compounds. However, with doses approximating the maximum tolerated dose, weight gains were similar to those of the pentachlorophenol and pentabromophenol. All survivors showed rapid weight gains when the drugs were omitted, and none of the animals exhibited symptoms of toxicity during this period.

Discussion

The toxicities of the compounds studied ranged in the following order: LD_{50} in mg. per kilo of Santobrite, 100; pentachlorophenol, between 125 and 200; and pentabromophenol, slightly more than 200. This compares with an LD_{50} of 150 for DDT (*3*), and 200 to 250 for chlordane (*4*).

Although little information is available on the other halogenated phenols reported in this paper, the pharmacology and toxicology of pentachlorophenol have received considerable study.

Early work on the toxic effects of pentachlorophenol was done by Bechold and Ehrlich (*5*). Recently extensive studies have been carried out by Kehoe, Deichmann, and Kitzmiller (*6*), Boyd, McGavack, Terranova, and Piccione (*7*, *8*), and Deichmann, Machle, Kitzmiller, and Thomas (*9*).

In extensive studies, Kehoe (*6*) and Deichmann and co-workers (*9*) reported the absorption, distribution, excretion, and acute and chronic toxicities of pentachlorophenol in several species of animals. Acute toxic effects included increased blood pressure, hyperglycemia and glycosuria, and hyperpyrexia and motor weakness. Lethal doses for single administration in the rabbit were 50 to 170 mg. per kilo of the free phenol and 250 mg. per kilo of the sodium salt when applied to the skin; 70 to 130 mg. per kilo of the phenol and 250–300 mg. per kilo of the salt administered orally. In the rat, the LD_{50} for single oral administration was 27 and 78 mg. per kilo for the free phenol in fuel oil and olive oil, respectively; for the sodium salt in water, it was 210 mg. per kilo.

Sodium pentachlorophenate was administered orally to 23 rabbits in doses of 3 mg. per kilo for 90 doses without signs of poisoning; the level of the drug in the blood did not increase after the fourth day. When administered to rats in the food in daily doses of 3.9 to 5 mg. per rat for 26 to 28 weeks, the only symptoms observed were lack of normal weight gains. This decreased food consumption was attributed to the unpleasant taste of the compound.

The above authors showed that approximately 70 percent of the orally administered sodium pentachlorophenate is excreted in the urine of rabbits in 24 hours, but 4 days are required for all traces to disappear from the blood (*9*).

Table 2. *Weight changes in survivors on acute toxicity experiments*

Series	Dose gm/kg	Number of animals	Number of survivors	Average weight of survivors—gm.								
				Days before administration				Days after administration				
				5th	4th	3d	0	1st	4th	5th	8th	9–23d
	Pentachlorophenol as a sodium salt											
1	0.125	10	10				94.3	93.5				125.8–20th.
	Pentachlorophenol as a copper salt											
2	0.650	10	6				84.7	89.0				160.0–21st.
	.400	10	6	91.2		96.2	112.7	115.2				120.0–9th.
	.200	10	10			81.9	95.6	98.4				147.4–20th.
	Pentabromophenol as a sodium salt											
3	0.300	10	1				138.0					175.0–17th.
	.200	10	6				127.8	125.5		131.8		162.8–18th.
	.150	10		68.1			76.8	81.6	93.3			111.8–16th.
	Santobrite											
4	0.150	10	1				90.0					145.0–21st.
	.100	10	5				111.5	105.3				154.8–20th.
	.050	10	10				101.7	95.6				130.7–20th.
	2,4,6-Tribromophenol as a sodium salt											
5	2.000	17	7				106.6	99.0				145.0–23d.
	1.000	20	17			82.1	99.3	97.1				128.7–20th.

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	2,4,6-Triiodophenol as a sodium salt [1]											
6	2.500	20	14		82.7		93.4	90.3			100.0	120.0–13th.
	1.500	20	20			99.5	117.6	112.4				158.5–20th.
	2,4,6-Triiodophenol as a sodium salt											
7	3.500	10	3				133.6	119.0				
	2.500	20	15				112.8	103.1				137.6–10th.
	1.500	18	18			126.0	135.9	125.2	133.7			174.8–23d.

[1] Supplied as the salt.

Table 3. *Subacute toxicity of halogenated derivatives of phenol in rats—oral administration*

Series	Dose gm/kg	Number animals	Death-Days						Percent mortality	Average daily weight—gm.								
										Days before administration				Days after administration				
			1st	2d	3d	4th	5th	6th–11th		5th	4th	3d	0	1st	2d	3d	4th	11th–20th
Pentachlorophenol as a sodium salt																		
(1)	0.150	10		1			3	2	60		78.0	80.5	91.9	93.9	92.0	92.1	93.7	124.5–15th.
	.100	10							0		67.8	69.0	77.9	80.8	83.3	87.7	89.6	116.7–16th.
Pentachlorophenol as a copper salt																		
(2)	0.650	10	4	4					80	80.1			86.2	88.8	90.5			120.0–11th.
	.400	20	9		2				55				91.9	91.7	87.5	90.2		118.5–13th.
	.200	10		1	1				20		79.9	82.5	96.1	99.3	97.4	99.6	101.5	135.3–15th.
Pentabromophenol as a sodium salt																		
(3)	0.250	10		1					10	72.9		77.7	97.4	99.0	100.2	99.3	103.9	127.1–15th.
	.150	10							0		65.5	66.9	73.8	78.5	81.0	85.3	90.2	109.6–16th.
Santobrite																		
(4)	0.100	10	5						50				113.0	102.6	97.6	107.0		152.8–20th.
	.050	10							0				105.2	96.8	94.7	99.6		128.9–20th.
	.025	10							0				79.5	82.6	86.3	87.1	89.5	108.1–16th.
2,4,6-Tribromophenol as a sodium salt																		
(5)	2.000	17	10	5		2			100				131.4	105.3	101.0	101.0		
	1.000	10		1	1	4		1	70		80.9	82.1	97.2	100.2	94.2	87.0	94.5	119.0–15th.
	.600	10							0		71.2	72.9	79.9	83.4	85.9	91.4	92.8	120.4–17th.

	2,4,6-Triiodophenol as a sodium salt [6]																	
(7)	2.500	10	2	7	1				100	76.0		84.7	99.8	95.5				
	1.500	20		3	3	2	6	1	75			99.8	115.1	110.3	107.1	100.9	92.8	110.0–11th.
	.650	10							0		66.8	71.5	77.4	80.8	82.8	90.0	92.0	128.6–16th.
	2,4,6-Triiodophenol as a sodium salt																	
(8)	2.500	15							100			105.5	113.7	104.0	89.0	96.0	88.0	
	1.500	10		1	1	1	3	1	70			125.3	133.3	125.2	126.0	121.9	112.4	138.5–11th.
	.650	10		1					10		65.9	70.1	78.8	79.4	85.8	89.6	88.2	124.7–17th.

[1] Moderate to severe congestion in the lungs with some petechial hemorrhages. Some areas of mild congestion in the lungs of survivors.

[2] Moderate to severe congestion in the lungs with hemorrhages. Some areas of mild congestion in the lungs of survivors.

[3] Petechial hemorrhages and congestion in the lungs. Some areas of mild congestion in the lungs of a few survivors on smaller doses, with most of them negative.

[4] Mild congestion in the lungs in some of survivors on largest doses. Most of survivors on smaller doses negative, with some areas of mild congestion in the lungs in a few.

[5] Congestion in the lungs with hemorrhages. Some areas of mild congestion in the lungs of survivors.

[6] Supplied as the salt.

[7] General hemorrhages in the lungs in most animals of largest doses, with severe inflammation, corrosion and hemorrhages in the mucous membrane of the pylorus and fundus of the stomach.

[8] Essentially same as 6.

Although some evidence of cumulation was shown by the rate of disappearance of pentachlorophenol from the blood, the evidence from previous work indicates that this compound is well tolerated on continued administration.

Summary and Conclusions

1. The systemic symptoms produced by toxic doses of pentachlorophenol were increased respiratory rate and amplitude, muscular weakness and collapse. In general, this syndrome was also produced by all the other related derivatives of phenol reported here except pentabromophenol. Pentabromophenol, in addition to the above symptoms, produced generalized tremors and occasional intermittent convulsions. In many respects the symptoms resembled those of DDT poisoning in the rat.

2. The acute toxicities of these compounds ranged in the following descending order: Santobrite, pentachlorophenol, pentabromophenol, the copper salt of pentachlorophenol, 2,4,6-tribromophenol, and 2,4,6-triiodophenol. Relatively no cumulative toxicity was produced by five consecutive daily doses of the first three compounds, but moderate cumulative effects were produced by the last three compounds under the same conditions.

3. Gross post-mortem findings were hemorrhages and congestion of the lungs, produced to a greater or lesser degree by all the compounds. Large doses of 2,4,6-triiodophenol produced severe inflammation, corrosion, and hemorrhages of the mucous membrane of the stomach. These were also produced to a lesser extent by 2,4,6-tribromophenol.

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Effect on Calves of Prolonged Oral Administration of Three Potential Molluscacides

By Jean R. Herdt,* Ladd N. Loomis,† and M. O. Nolan*

Investigators in the Laboratory of Tropical Diseases for several years have screened chemicals in an effort to develop molluscacides for the destruction of the snail intermediate hosts of the human schistosomes. Certain compounds that were active against snails in the screening tests were tried under natural conditions in Texas (*1*) and Puerto Rico (*2*). In the Texas tests, two pentahalogenated phenols, pentabromophenol and sodium pentachlorophenate, showed promising molluscacidal activity. In Puerto Rico, these same two compounds together with other halogenated chemicals, copper pentachlorophenate, 2,4,6-tribromophenol, 2,4,6-triiodophenol and its sodium salt, proved to be very effective molluscacides.

The trials in Texas and Puerto Rico were intentionally limited because of the lack of information on the toxicity for mammals of many of the compounds which were tested as molluscacides. The experience in Puerto Rico laid the groundwork for more extensive field trials and emphasized the desirability of obtaining information on the toxicity to mammals of the more promising molluscacides.

The molluscacidal chemicals used in this work are reported on elsewhere in this issue by Stohlman, who studied their acute and chronic effects on rats. In addition, extensive investigations with experimental animals have been conducted by a number of workers over a period of years on the toxicology of pentachlorophenol and sodium pentachlorophenate, which appear to be the most promising molluscacides for use in the field. Results of these investigations have been summarized by the Monsanto Chemical Company (*3*).

In the trials in Puerto Rico (*2*), two mammalian tests were conducted before molluscacidal tests were made with sodium pentachlorophenate in flowing water. A rhesus monkey was given 200 cc. of water containing 20 parts per million of sodium pentachlorophenate without exhibiting any visible symptoms of toxicity. In another experiment a calf drank 40 gallons of water containing 20 ppm of the compound over a period of 4 days without suffering ill effects.

In the present experiment, information was sought on the effects of

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prolonged oral administration to calves of the three pentahalogenated phenols which were tried as molluscacides in Puerto Rico.

Methods and Materials

Test animals were three young bulls, weighing at the beginning of the experiments between 164 and 210 pounds and at the termination between 247 and 296.5 pounds. Since no control animal was available, the experimental animals were observed for 2 weeks (July 10 to 24) before chemical dosage was begun. Routinely, on each weekday of the 2-week observation period, pulse, respiration rate, and rectal temperature were taken, and urinalyses were made for sugar and albumin. Several blood examinations were made for cell enumerations and differential counts prior to dosage. The averages of data gathered during this period were used as the norm.

Sodium pentachlorophenate, copper pentachlorophenate, and pentabromophenol, respectively, were given orally to the calves in their drinking water. The daily dosages were well in excess of the concentration at which the chemicals are effective molluscacides. In the field, the molluscacides were applied to both standing and flowing waters at the maximum rate of 10 parts per million. It was arbitrarily decided that the optimum range of dosage in parts per million for the calves should be not less than 40 and not greater than 60. Accordingly, daily dosages were at the rate of 7.6 milligrams per kilogram of body weight, based on original body weights. After several days of less than normal water consumption by the calves, the quantities of chemicals and water were so adjusted that the chemical concentration in 10 liters of water consumed daily by each calf was maintained, as follows: for the calf given sodium pentachlorophenate, at 60 ppm; for the calf given copper pentachlorophenate, at 51 ppm; and for the calf given pentabromophenol, at 46.5 ppm.

Sodium pentachlorophenate, which is readily soluble in water, was stirred directly into the drinking water. Copper pentachlorophenate and pentabromophenol, which are almost entirely insoluble in water, were dissolved in alcohol and acetone, respectively; 70 ml. of the solvent together with 5 ml. of Tween 80 being used in every 10 liters of water administered to the calves.

The chemical dosages were given daily (including Saturday and Sunday) to the calves for 5 weeks (July 24–August 28). During this period of uninterrupted dosage, records were kept daily (excluding Saturday and Sunday) of pulse, respiration rate, and rectal temperature. Urinalyses were made daily with few exceptions when it was impossible to collect samples of urine. Blood was drawn three times a week and records were kept of red and white cell counts and differential counts.

Necropsy of the calf given copper pentachlorophenate was performed 4 days after cessation of the 5-week period of daily dosage.

Dosage of the other two calves was resumed after a lapse of 4 days and was continued an additional week for the calf given pentabromophenol and two additional weeks for the calf given sodium pentachlorophenate. Both of these calves were necropsied 4 days after termination of the additional dosage.

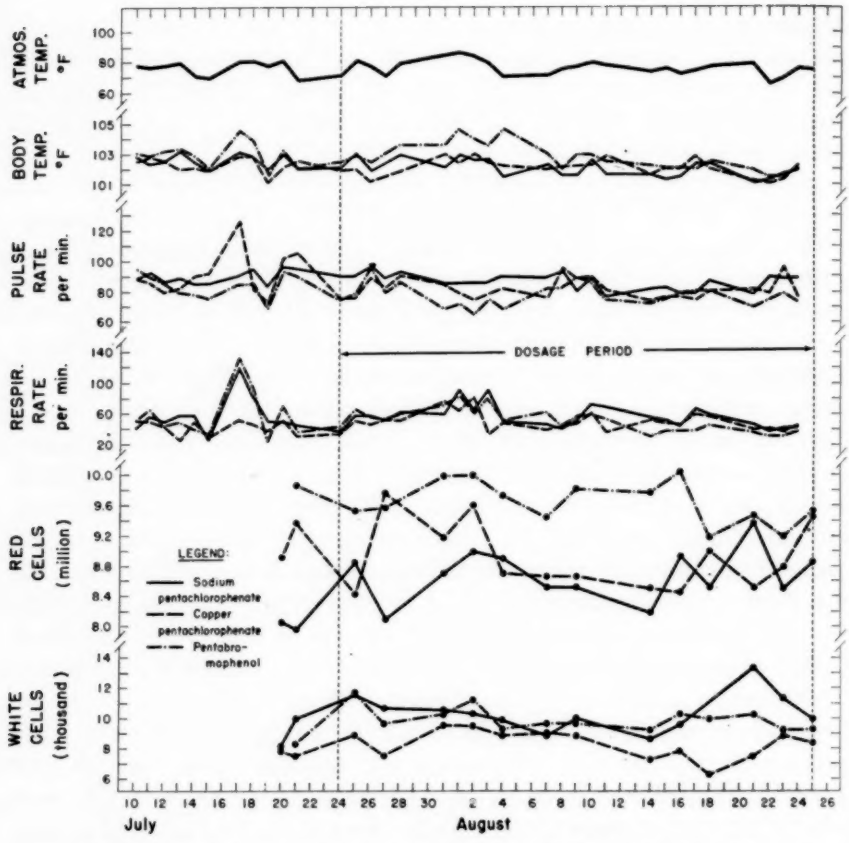
Results and Conclusions

The data on atmospheric and body temperatures, pulse and respiration rates, and blood counts are presented in the accompanying graph. Observations covering the 5-week period of uninterrupted dosage displayed no marked or significant deviations from the normal. Body temperatures of all three animals remained within normal limits during the experimental period, and although there was a slight extended depression of the body temperature of the calf given sodium pentachlorophenate after the administration of the chemical, no significant trends became evident. Pulse and respiration rates, through varying widely, fell within the normal range. On the days when the respiration rate was accelerated, it was usually true that the atmospheric temperature was somewhat above average and/or that the animals were exceptionally active and difficult to control.

The dates on which blood examinations were made are represented in the graph by heavy dots. Berkson et al. (*4*) demonstrated the tremendous variation possible in accurately performed hemocytometic measurements. In view of their work, the variations in cell enumerations in this experiment, though large, were within the bounds set by them as possible experimental error. The differential counts, not included in the graphs, were also within the expected limits of variation and showed no significant trends. The variation in the counts was large but was approximately the same for all three calves. The range of percentages for the various white cells (*a*) before dosage and (*b*) during dosage, was as follows: lymphocytes (*a*) 64–69, (*b*) 56–82; neutrophils (*a*) 20–34, (*b*) 13–35; monocytes (*a*) 1–4, (*b*) 1–11; eosinophils (*a*) 0–4, (*b*) 0–5; basophils (*a*) 0–2, (*b*) 0–2.

The urinalyses showed a positive dextrose reaction (less than 0.1 percent) rather consistently, but tests for albumin were negative throughout the course of the experiment. Prior to chemical dosage, the urinalyses were with few exceptions negative for dextrose and albumin.

Post-mortem examinations of the tissues revealed no toxic reactions to the drugs. Grossly, all three calves appeared normal with the exception of a slight enteritis, or congestion of the mucosa of the small intestine. Formalin (10 percent) and Zenkers were used as fixatives, and death to fixation of the tissues was 0 hour. Microscopically, sections of the heart, lungs, liver, spleen, thymus, adrenals, muscle, and lymph nodes showed no significant lesions. The brain of the calf given sodium pentachlorophenate showed no lesions. The



Physiological data on three calves prior to and during dosage with pentahalongenated phenols.

small intestines of all three calves showed some congestion of the capillaries of the villi but no hemorrhage was seen. A few helminth ova were noticed.

Following necropsy of the calves, the meat was hung in a well-ventilated cold room at a temperature of 37° F. for 1 week. It was then butchered and distributed to various individuals. Some of it was frozen and held for varying periods before it was cooked and eaten. The brains, liver, heart, kidneys, and thyroid glands were distributed immediately after necropsy. At least 60 persons ate the various organs and the meat. The persons who received the meat were told that the calves had been given a daily dose of a specific chemical over a period of at least 5 weeks and were asked to report upon the flavor of the meat as well as ill effects, if any, that might develop after its consumption. All reports were favorable; the meat was excellent and there were no immediate or delayed clinical symptoms.

Molluscacides are applied to natural waters in the field, as mentioned above, at a calculated dosage of 10 ppm. There is quick dissipation of the chemicals with marked dilution throughout the waters, particularly in flowing streams. All necessary precautions are taken to guard against access by humans and cattle to the waters at or near the site of application where the chemical concentration is heaviest. From a practical standpoint, it is unlikely that cattle drinking natural waters treated with chemical molluscacides would be exposed to concentrations of chemical in as high a range as 40 to 60 ppm and certainly not for any extended period of time. In view of the nontoxic reactions of the calves in the present experiment to equivalent dosages of the pentahalogenated phenols administered to them daily in their drinking water over a period of at least 5 weeks, it would appear that pentabromophenol and the copper and sodium salts of pentachlorophenol have an adequate margin of safety for use in the field as molluscacides.

Summary

The effect on cattle of repeated sublethal doses of three potential molluscacides, sodium pentachlorophenate, copper pentachlorophenate, and pentabromophenol was determined. The chemicals were given to three young bulls in their drinking water at a dosage of 7.6 mg./kg./day for at least 5 weeks. No significant deviations from normal were found in pulse, respiration rate, temperature, urinalyses, or in blood counts. Post-mortem examinations revealed no toxic manifestations. It is believed that these halogenated phenols can be used with safety as molluscacides in the field provided reasonable precautions are taken in their application.

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Double Infection of the Rat Fleas *X. cheopis* and *N. fasciatus* With *Pasteurella* and *Salmonella*

By C. R. Eskey, M.D., Frank M. Prince, B.S., Frank B. Fuller, M.S.*

During the course of experiments with plague-infected fleas, *Xenopsylla cheopis* (Roth.) and *Nosopsyllus fasciatus* (Bosc.), a number of both species accidentally became infected with *Salmonella enteritidis* (Gaertner) which was present among recently acquired white mice. As none of the secondarily infected fleas transmitted plague, although several developed complete blockage of the stomach, it was surmised that the *Salmonella* bacteria might have had some inhibitory action that interfered with plague transmission. The experimental work reported herein was undertaken to investigate the question in more detail. *Salmonella typhimurium* (Loeffler) was included in the study because it is also a widespread rodent infection.

Infection of Fleas

Fleas were infected with both plague and *Salmonella* by feeding them on white mice that had been previously inoculated subcutaneously with 0.1 cc. of a 24-hour tryptose hormone broth culture. The reaction of different mice to infection varied greatly so that it was necessary to inoculate from 5 to 10 animals at a time in order to be sure of obtaining 1 mouse suitable for infecting fleas. Only mice having a bacteremia of five or more organisms per microscopic field in smears made by snipping off the ends of the tails were utilized for infecting fleas.

The control fleas referred to in the following discussion were infected only with plague. They were kept under the same conditions and tested at the same time as most of the other infected fleas.

Determining Flea Infection

As soon as feces were observed in the bottom of each flea's test tube following its exposure to infection, the flea was transferred to a clean test tube. Then the fecal material was emulsified in a drop of bouillon and streaked on a tryptose blood agar plate. If the infecting bacteria did not appear on the first plate, a second fecal test was made before discarding the flea as uninfected. Fecal plate cultures were carried out once a week or oftener as long as the infected

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flea lived. After death, the body of each flea was triturated in a drop of bouillon, and plate cultures were prepared as described above.

Flea infection with either of the *Salmonella* organisms, whether alone or complicated by *Pasteurella pestis*, can be readily determined by the bacteriological procedures mentioned above. This is also true of uncomplicated plague infection; but when associated with salmonellosis, it is frequently impossible to prove the presence of *P. pestis* by either culture or inoculation tests. However, the positive diagnosis of plague infection of fleas does not necessarily require the demonstration of *P. pestis* by bacteriological methods because the presence of this infection can be determined by the microscopical demonstration of dark masses in the stomachs or proventriculi of live fleas when they are examined a short time after having ingested a blood meal (*1*). The *Salmonella* infections do not produce masses simulating those produced by the plague bacillus (*2*) nor do they prevent the formation of the masses which are characteristic of *P. pestis* infection. Furthermore, the mass formations of some doubly infected fleas which gave negative bacterial tests for *P. pestis* developed complete obstruction of the stomach with the typical microscopical picture of plague blockage. A few of these blocked fleas transmitted plague as illustrated in the following instance.

An *X. cheopis* female (XTP–138) was infected with *S. typhimurium* and 2 days later was fed on a plague-infected mouse. During the next 30 days, or until death of the flea, seven plague cultures were made of the feces, and then one plague culture was made of its body. Not a single *P. pestis* colony was found on any plate, but numerous colonies of *S. typhimurium* were present on all of them. At the time of the first microscopical examination on the fourth day following exposure to plague, a small dark area was observed in the blood-distended stomach. This formation had the characteristic appearance of an early plague mass. The progress of the mass was followed microscopically at 4- to 5-day intervals until the twenty-eighth day when typical plague-blockage of the stomach, due to the mass invading the proventriculus, was observed. After the development of complete obstruction of the stomach, the flea was allowed to bite three mice, two of which died of plague 5 days later so that there can be no question regarding whether or not this flea was infected with plague, although *S. typhimurium* was the only organism that could be demonstrated in cultures.

Additional evidence proving that the presence of *P. pestis* in the gastrointestinal tract of fleas may be completely obscured by an associated *Salmonella* infection was provided by the fecal tests of two *N. fasciatus* that ceased to excrete *S. typhimurium* 25 and 31 days, respectively, after the fleas had fed on a plague-infected mouse. No colonies of *P. pestis* were found on the culture plates until after the

Salmonella organisms disappeared, and then a very few colonies of plague bacilli were found on the next plate with the number becoming more numerous on the succeeding plates.

The microscopical demonstration of dark masses of the type characteristic of plague infection in the proventriculi or stomachs was the sole basis for considering 30 percent of the fleas dealt with herein as harboring both plague and *Salmonella*. The presence of the latter organisms was always proved by culture. The diagnosis of double infection in the balance of the fleas was based on finding *P. pestis* in the feces at least once, or in cultures of the dead fleas. *P. pestis* was found only once in the feces of 40 percent of the fleas, while in nine instances the bodies of the fleas proved to be plague infected when all fecal cultures gave negative results.

Two factors appear to have been responsible for the poor results obtained in attempting to prove the presence of *P. pestis* in combination with *Salmonella* bacteria by culture tests. The more important factor seemed to be the inhibiting action of salmonellosis on the multiplication of plague bacilli in the gastrointestinal tract so that very few *P. pestis* were present in the feces of fleas harboring the double infection in comparison with the number usually excreted by those infected solely with plague. Secondarily, the number of *Salmonella* organisms found on most culture plates and their rapid or profuse growth must have obscured the few plague colonies present on many cultures. The same effect was produced in broth cultures by adding 0.1 cc. of a 24-hour culture of *Salmonella* bacilli to 5 cc. of a 24-hour culture of plague. After 48 to 72 hours incubation of the mixture, *P. pestis* could no longer be found on tryptose blood agar plates.

Handling Infected Fleas

During the different stages of this study, the mean temperature at which fleas were kept varied from 71.5° to 74° F. Each flea was given an opportunity to feed on the clipped abdomen of a healthy mouse every day except Sundays and holidays. From three to five fleas were fed on the same mouse five to six times, or until one of the fleas became blocked; then the mouse was set aside for 5 days' observation. All mice that survived for 5 days were killed, autopsied, and routine cultures made from the liver, spleen, and heart's blood.

After a flea started to bite, the technician examined it at frequent intervals with a hand lens, using a pencil-point flashlight for illumination. Whenever it appeared that the host's blood was not entering the stomach normally, the flea was subjected to a microscopical examination to determine whether or not blockage of the stomach had developed. Any mouse that had been exposed to the bite of a flea found to be blocked was set aside for observation.

Transmission of Infection

By X. cheopis

According to the criteria outlined above for determining flea infection, 126 *X. cheopis* were infected with combined plague and *Salmonella* during this investigation. Of this number, 13 transmitted plague; 3, plague and *Salmonella* at the same time; 7, *S. enteritidis;* and 8, *S. typhimurium*. One blocked *X. cheopis* transmitted plague to a mouse one day and *S. typhimurium* to another the next day.

The complete details regarding the transmission of infection by *X. cheopis* are given in percentages in table 1. From these figures it will be observed that a slightly greater percentage of *X. cheopis* transmitted *S. enteritidis* than *S. typhimurium*, and that a slightly larger, but not significantly different, percentage of plague transmissions was obtained with fleas infected with *P. pestis* and *S. enteritidis* than with those infected with *P. pestis* and *S. typhimurium*. On the other hand, and contrary to expectations, the fleas infected primarily with plague or those in which plague mass formations had an opportunity to form before being infected with *Salmonella* proved to be slightly less effective vectors of plague and better transmitters of salmonellosis than the fleas secondarily infected with *P. pestis*. From the percentages listed in table 1, it might be construed that *X. cheopis* were better vectors of plague than *Salmonella* because the fleas that transmitted both infections at the same time are included with those that transmitted only plague. In reality, two more *X. cheopis* transmitted *Salmonella* than plague.

By comparing the figures in the last two lines of table 1, it will be noted that *X. cheopis* infected with *P. pestis* and *Salmonella* were relatively poor vectors of plague in comparison with those infected with only *P. pestis*. Actually *X. cheopis* females proved to be three and one-half times and males four times more likely to transmit plague

Table 1. *Transmission of infection by* X. cheopis *according to different combinations of flea infection with a comparison of the results obtained with control fleas infected with uncomplicated plague*

Nature of *X. cheopis* infection	Number *X. cheopis* infected		Percent transmitting plague or both plague and *Salmonella*		Percent transmitting *Salmonella*	
	Female	Male	Female	Male	Female	Male
Plague, then *S. enteritidis*	17	28	[1] 5.9	14.3	23.5	7.1
Plague, then *S. typhimurium*	31	12	12.9	8.5	19.4	
Total primary plague	48	40	10.4	12.5	20.8	5
S. enteritidis, then plague	4	4	[1] 50.0		25.0	
S. typhimurium, then plague	13	17	[1] 30.8		15.5	
Total secondary plague	17	21	35.3		17.6	
Total plague and *S. enteritidis*	21	32	14.3	12.5	23.8	6.2
Total plague and *S. typhimurium*	44	29	18.2	3.4	18.2	
Total plague and *Salmonella*	65	61	16.8	8.2	20.0	3.3
Uncomplicated plague infected	73	32	56.9	31.3		

[1] 1 female transmitted plague and *Salmonella* at the same time.

when their infection was not complicated with *Salmonella* than when the fleas harbored both infections. If equal numbers of male and female *X. cheopis* are infected with *P. pestis* and *Salmonella*, 12.5 percent of the total infected would be expected to transmit plague according to the results of these experiments, while 44 percent of those infected with uncomplicated plague would be vectors of the disease under the same experimental conditions.

By N. fasciatus

The results of transmission experiments with *N. fasciatus*, as itemized in table 2, were similar in many respects to those obtained with *X. cheopis*, except that *N. fasciatus* was the less effective vector. This was especially evident in the case of male *N. fasciatus*, as none of the 25 infected with both plague and *Salmonella* transmitted either infection, whereas 5 of 61 doubly infected male *X. cheopis* acted as vectors of plague and 2 as vectors of *Salmonella*. Plague transmission by *N. fasciatus* was limited to two females, both of which were infected with *S. typhimurium* and then secondarily with *P. pestis*. The failure of any of the primarily plague-infected *N. fasciatus* to transmit plague emphasizes and corroborates similar results obtained with *X. cheopis*. Furthermore, as in the case of the latter species, doubly infected *N. fasciatus* proved to be better vectors of salmonellosis than plague.

The inhibitory action of a complicating *Salmonella* infection upon the possibilities of doubly infected *N. fasciatus* transmitting plague is clearly demonstrated by the figures in table 2. According to the experimental data in this table, female *N. fasciatus* infected with *P. pestis* and *Salmonella* were only one-eighth as likely to transmit plague as females infected only with *P. pestis*. Furthermore, none of the doubly infected males acted as vectors as compared to 8 percent transmissions by males harboring uncomplicated plague. According to experimental findings, if an equal number of female and male

Table 2. ***Transmission of infection by* N. fasciatus *according to different combinations of flea infection with a comparison of the results obtained with control fleas infected with uncomplicated plague***

Nature of *N. fasciatus* infection	Number *N. fasciatus* infected		Percent transmitting plague or plague and *Salmonella*		Percent transmitting only *Salmonella*	
	Female	Male	Female	Male	Female	Male
Plague, then *S. enteritidis*	9	4	----------	----------	22.2	----------
Plague, then *S. typhimurium*	17	7	----------	----------	11.8	----------
Total primary plague	26	11	----------	----------	15.4	----------
S. typhimurium, then plague	25	14	[1] 8	----------	4	----------
Total plague and *S. typhimurium*	42	21	4.8	----------	7.1	----------
Total plague and *Salmonella*	51	25	3.9	----------	9.8	----------
Uncomplicated plague	15	13	33.3	7.7	----------	----------

[1] 1 female transmitted both plague and *Salmonella* at the same time.

N. fasciatus were infected with both *P. pestis* and *Salmonella*, only 2 out of 100 could be expected to transmit plague, or a vector potential too low for the continued propagation of the disease among a rodent population. This inhibitory effect of a *Salmonella* infection upon plague transmission by *N. fasciatus* was approximately six times greater than noted above for *X. cheopis*.

Stomach Blockage and Transmission of Infection

Blockage or obstruction of the stomach due to mass formations in the proventriculus or esophagus was present at the time all doubly infected *X. cheopis* and *N. fasciatus* transmitted plague to exposed mice. All *X. cheopis* were also blocked at the time they transmitted salmonellosis, but no evidence of obstructing masses was observed for three *N. fasciatus* that transmitted this infection. The mechanism involved in the transmission of *Salmonella* by these three *N. fasciatus* was probably the same as that involved in its transmission by fleas, infected solely with *Salmonella* organisms (*2*), which acted as vectors without the formation of visible blocking masses.

Since blockage appears to be essential for doubly infected fleas to act as vectors of plague, it is evident from a comparison of the figures in table 3 that a complicating *Salmonella* infection tends to reduce the possibilities of plague transmission by interfering with mass formations producing obstruction of the stomach. This table has been computed for females only because of the difference in the number of each sex tested and because females proved to be much more efficient vectors of infection than males. The most noticeable feature in table 3 is the greater deterrent effect of a complicating *Salmonella* infection upon blockage of *N. fasciatus* than upon *X. cheopis*. In fact, the presence of *Salmonella* organisms reduced blockage of *N. fasciatus* females to one-fourth the percentage of those infected only with plague, while blockage of doubly infected *X. cheopis* females was much less affected, being reduced only 15 and 30 percent, respectively,

Table 3. *Relation of blockage of the stomach to plague transmission by female* X. cheopis *and* N. fasciatus

	Nature of female infection					
	X. cheopis females			*N. fasciatus* females		
	Plague then *Salmonella*	*Salmonella* then plague	Plague only controls	Plague then *Salmonella*	*Salmonella* then plague	Plague only controls
Number infected	48	17	73	26	25	15
Number that became blocked	34	10	61	4	4	9
Percent blocked	70.8	58.8	83.6	15.4	16.0	60.0
Percent blocked transmitting plague	14.7	60.0	68.9	----------	50.0	55.5

for those females secondarily and primarily infected with *Salmonella* as compared to the controls.

This marked difference in the effects of *Salmonella* infection upon blockage of the two varieties of fleas is probably due to the difference in the mechanism involved in producing obstruction of the stomach in the majority of each species. In the case of *N. fasciatus*, as well as most other species of fleas, plague masses commonly originate in the stomach so that blockage depends upon the mass formations invading the proventriculi secondarily which may not occur for several weeks or months. On the other hand, plague masses tend to originate and to mature in the proventriculi of most *X. cheopis*, thus, in comparison with stomach masses, insuring blockage of a greater percentage of fleas and shortening the period between infection and obstruction. Therefore, it would appear that mass formations developing in the stomachs of *N. fasciatus* would be more exposed to the effects of a complicating *Salmonella* infection which, as shown above, tends to inhibit blockage of doubly infected females of both species.

The restraining action upon blockage by a complicating *Salmonella* infection appears to have been chiefly responsible for the low plague vector efficiency of all doubly infected *N. fasciatus* females and for *X. cheopis* females that were secondarily infected with *P. pestis*. But, the failure of most primarily plague-infected *X. cheopis* females to transmit this infection did not depend as much upon the percentage that developed obstruction of the stomach as upon the innocuousness of their blocked bites. Therefore, it may be stated that a complicating *Salmonella* infection reduces the effectiveness of doubly infected *X. cheopis* and *N. fasciatus* to act as transmitting agents of plague by interfering with blockage of the stomach and by rendering many blocked bites harmless in regard to plague transmission.

Salmonella-Infected Fleas Collected

No reference could be found in the literature regarding the *Salmonella* infection of fleas collected from either domestic rats or wild rodents. However, during the past year the Western Communicable Disease Center Laboratory, in the course of testing fleas for plague infection by guinea pig inoculation, found that 10 specimens of fleas from wild rodents and 7 from domestic rats were infected with *Salmonella* as summarized in table 4. More specimens of fleas infected with *S. typhimurium* than *S. enteritidis* were obtained from both wild rodents and domestic rats. In fact, only one flea specimen collected from wild animals, namely chipmunks, was infected with *S. enteritidis*. All bacteriological identifications were verified by the Communicable Disease Center Enteric Laboratory, Chamblee, Ga.

All test guinea pigs died from the effects of the *Salmonella* infections in 3 to 7 days, except one that was inoculated with *S. enteritidis*-

Table 4. *Summary of data concerning the demonstration of rodent flea infection with salmonellosis*

Locality where obtained	Fleas inoculated	Rodent source of fleas	
		Number	Species
S. typhimurium			
New Mexico, San Juan County	46	6	Prairie dogs, *C. gunnisoni.*
Montana, Richland County	61	35	Prairie dogs, *C. ludovicianus.*
Wyoming, Fremont County	19	11	Prairie dogs, *C. leucurus.*
Idaho, Caribou County	565	12	Marmots, *M. flaviventris.*
New Mexico, Rio Arriba County	61	103	Deer mice, *P. maniculatus.*
New Mexico, McKinley County	12	79	Do.
Montana, McCone County	17	25	Do.
Wyoming, Lincoln County	9	19	Do.
Kansas, Wichita County	1	16	Harvest mice, *R. megalotis.*
California, San Francisco	6	4	Norway rats, *R. norvegicus.*
Do	6	8	Do.
Do	75	15	Do.
Washington, Tacoma	48	2	Do.
Do	26	30	Roof rats, *R. rattus.*
S. enteritidis			
Wyoming, Washakie County	5	7	Chipmunks, *E. minimus.*
New Mexico, Bernalillo County	310	116	Norway rats, *R. norvegicus.*
Washington, Seattle	9	1	Do.

infected fleas from chipmunks, so that there is no question regarding the high degree of virulence of this infection among wild and domestic rodents. Furthermore, it would seem that epizootics of this disease are widely disseminated among rodents in the western part of the United States.

Discussion

It is evident from the foregoing report that the two species of domestic rat fleas, *X. cheopis* and *N. fasciatus*, can be readily infected with *P. pestis* and with *S. typhimurium* or *S. enteritidis*. A few ground squirrel fleas, *Diamanus montanus*, have been infected with plague and *Salmonella* so that it may be assumed that most other flea species are susceptible to double infection with these bacteria.

Fleas infected with both *P. pestis* and *Salmonella* organisms proved to be slightly better vectors of salmonellosis than plague, but in comparison to controls or those infected only with *P. pestis*, the doubly infected fleas were relatively poor transmitting agents of plague. For instance, according to the experimental results, only 12.5 percent of an equal number of doubly infected *X. cheopis* males and females are likely to transmit plague as compared to 44 percent transmissions by controls. The inhibiting action of the complicating *Salmonella* infection upon plague transmission by *N. fasciatus* was even greater than in the case of *X. cheopis*. None of 25 doubly infected *N. fasciatus* males transmitted plague, while transmissions by females were limited to 4 percent as compared to 33 percent of the controls. From these findings it may be assumed that a complicating *Salmonella* infection is likely to reduce the vector efficiency of doubly infected *X. cheopis* to such a degree that such fleas will be incapable of propa-

gating a plague epizootic and may not be able to keep the disease alive in an enzootic form except under very favorable conditions. On the other hand, the inhibiting effects of a *Salmonella* infection upon *N. fasciatus* was so great that it seems unlikely that doubly infected fleas of this species would be able to keep rodent plague infection active under any circumstances.

The wide distribution of rodent salmonellosis is evident from the fact that infected fleas were obtained from 7 species of wild rodents which were shot or trapped in 10 counties of 5 Western States and from 2 species of domestic rats that were trapped in 3 Pacific Coast ports and a hog ranch near Albuquerque, N. Mex. All fleas from the last source were chicken fleas, *Echidnophaga gallinacea*.

The collection of *Salmonella*-infected fleas from domestic rats and several species of wild rodents, which were shot or trapped in widely scattered areas of the western part of the United States, indicates that epizootics of salmonellosis must be rather common in urban and rural areas. Furthermore, this evidence proves that fleas may be naturally infected with either *S. typhimurium* or *S. enteritidis*. Therefore, although there is no definite evidence to support the theory, it may be assumed that should epizootics of plague and salmonellosis involve the rodents of the same rural area or urban community, the course of the plague epizootic might be adversely affected by the concurrent salmonellosis.

Summary

This investigation demonstrated that the domestic rat fleas, *X. cheopis* and *N. fasciatus*, can be infected with combined plague and *Salmonella*, and that such fleas may transmit either infection. However, the ability of these doubly infected fleas to transmit plague was greatly inhibited by the complicating *Salmonella* infection.

Naturally *Salmonella*-infected fleas were collected from domestic rats and several species of wild rodents in many different areas in the Western States, thus demonstrating the wide dissemination of salmonellosis among rodents. It is possible that *Salmonella* epizootics may sometimes modify the course of plague among a rodent population subjected to both infections.

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Two Provisional *Shigella boydii* Serotypes

By W. H. Ewing and M. W. Taylor*

Provisional *Shigella boydii* 10

Szturm, Piéchaud, and Neél (*12*) described two cultures that were isolated from acute cases of bacillary dysentery in Madagascar. These cultures, D15 and D21, presented biochemical characteristics similar to those given by *Shigella boydii* types but antigenically were unrelated to previously described shigellae. It was concluded that the two cultures comprised a new *S. boydii* serotype. The writers obtained cultures D15 and D21 for study and comparison with several undescribed *Shigella* and *Shigella*-like cultures in our collection. It was found that cultures D15 and D21 biochemically and serologically were similar to two microorganisms, cultures 430 and 650, that were isolated by the senior author from cases of bacillary dysentery in Italy during 1944.

The biochemical reactions obtained with cultures D15, D21, 430, and 650 are as follows: glucose, mannitol, and arabinose are fermented without gas formation within 24 hours, and acid is produced from dulcitol after 1 to 4 days' incubation. The cultures vary in their ability to utilize maltose. Lactose, sucrose, rhamnose, salicin, adonitol, and inositol are not utilized. The microorganisms are nonmotile, do not hydrolyse urea, do not form acetylmethylcarbinol, do not grow on Simmons' citrate agar, do not utilize citrate in the medium of Christensen (*2*), and do not form indol. The methyl red test is positive.

Cultures D15 and D21 of Szturm et al. (*12*) are agglutinated to the titer of antiserums prepared with cultures 430 and 650. Conversely, cultures D15, D21, 430, and 650 reacted similarly in an antiserum prepared with a heated (100° C., 2½ hours) broth suspension of culture D21. The results of reciprocal agglutinin absorption tests indicate that the heat-stable somatic antigens of these four cultures are identical. Results representative of these tests are given in table 1. The cultures that comprise this type are unrelated, in any significant way, to described *Shigella* types. However, the serotype is related to provisional *Shigella boydii* 11, described below.

Studies on the relationship of provisional *S. boydii* 10 cultures to other members of the family Enterobacteriaceae revealed that the O antigens of provisional *S. boydii* 10 cultures are related to those of

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Table 1. *The antigenic relationship of provisional* S. boydii *10 cultures and* E. Coli *O group 105*

O antigen suspensions (100° C., 1 hr.)	O antiserums						
	D21			430		*E. coli* 0105	
	Unabsorbed	Absorbed by		Unabsorbed	Absorbed by D21	Unabsorbed	Absorbed by D21
		430	*E. coli* 0105				
D21 (Szturm et al)	[1] 20, 480	[2] 0	5, 120	20, 480	0	1, 280	0
430 (Italy)	5, 120	0	2, 560	20, 480	0	1, 280	0
E. coli 0105	5, 120	0	0	2, 560	0	20, 480	10, 240

[1] Figures indicate the reciprocal of the highest dilution that gave visible agglutination.
[2] 0 indicates negative in a dilution of 1:40 and higher.

Escherichia coli O group 0105 [1] but are not identical with them (table 1).

Provisional *Shigella boydii* 11

Culture 34 represents the first culture of the second provisional *S. boydii* type that was seen by the writers. It was isolated by the senior author from a case of bacillary dysentery in Oran, Algeria, in 1943. Culture 732 was isolated by Dr. A. H. Stock in Casablanca during 1943. Culture 6108/50 was recovered from a case of dysentery, complicated by a *Giardia* infestation, at the Public Health Service Outpatient Clinic, Washington, D. C., and was sent to this laboratory for examination. The patient from whom culture 6108/50 was isolated became ill upon his return to the United States from South and Central America. Dr. Rebelo isolated culture 606/51 in Mexico City and sent it to this laboratory for identification. The history of this culture is not available.

The biochemical reactions of cultures 34, 732, 6108/50, and 606/51 are similar to those of cultures D15, etc. except that dulcitol is not utilized and indol is formed.

Cultures of this serotype are related to *Shigella boydii* 4 (P274) and to Alkalescens-Dispar O group 1 (*Shigella alkalescens*). The factor that is common to these three types is the factor that relates *S. boydii* 4 and Alkalescens-Dispar (A–D) 01 cultures. Cultures of provisional *S. boydii* 11 no longer react in antiserum for *S. boydii* 4 that is absorbed with a suspension of A–D 01 nor in antiserum for A–D 01 that is absorbed with a culture of *S. boydii* 4. Provisional *S. boydii* 11 cultures contain an O antigen in common with provisional *S. boydii* 10 cultures, but each of these serotypes contains a specific antigen that is not shared (table 2). This relationship may be explained by use of the arbitrary formula, *a b c*. The two serotypes

[1] For studies on serological typing of *Escherichia coli* cultures see references *4, 7–11*.

Table 2. *The relationship of provisional* S. boydii *10 and provisional* S. boydii *11 cultures*

O antigen suspensions (100° C., 1 hour)	O antiserums			
	Provisional *S. boydii* 10 (430)		Provisional *S. boydii* 11 (34)	
	Unabsorbed	Absorbed by 34	Unabsorbed	Absorbed by 430
Provisional *S. boydii* 10 (430)	20, 480	5, 120	10, 240	0
Provisional *S. boydii* 11 (34)	1, 280	0	20, 240	2, 560

contain the antigen *a* in common, and each type contains an unrelated antigen which may be designated *b* in provisional *S. boydii* 10, and *c* in provisional *S. boydii* 11 cultures. To separate these two serotypes by means of slide tests, it is necessary to employ antiserums that are cross absorbed. Cultures of provisional *S. boydii* 11 are not related significantly to other known shigellae. Provisional *S. boydii* 11 cultures contain heat-stable somatic antigens that are identical with those of *E. coli* O group 105, as demonstrated by reciprocal agglutinin absorption tests (table 3).

Table 3. *The relationship of provisional* S. boydii *11 and* E. coli *O group 105*

O antigen suspensions (100° C., 1 hour)	O antiserums			
	Provisional *S. boydii* 11 (732)		*E. coli* 0105	
	Unabsorbed	Absorbed by *E. coli* 0105	Unabsorbed	Absorbed by provisional *S. boydii* 11 (732)
Provisional *S. boydii* 11 (732)	5, 120	0	5, 120	0
E. coli 0105	5, 120	0	20, 480	0

Discussion

The results of our studies confirm and extend those of Szturm et al. (*12*). Cultures D15, D21, 430, and 650 are unrelated to known shigellae and constitute a new serotype. Since the cultures utilize mannitol but bear no serological relationship to *Shigella flexneri* serotypes, it is necessary to place them in group C, the *Shigella boydii* group,[2] as suggested by Szturm and associates (*12*). Therefore, we propose to designate this new serotype provisional *Shigella boydii* 10. Pending confirmation and agreement of other workers, this serotype

[2] Group C of the *Shigella* schema consists of *Shigella boydii* 1 through 7 (*5*). Type 112 described by Cox and Wallace (*3*) was accepted by the Shigella Commission of the Enterobacteriaceae Subcommittee as provisional *Shigella boydii* 8, and type 1296/7 (*1*) was accepted as provisional *Shigella boydii* 9 (*6*).

will be added to the *Shigella* schema when the report of the Enterobacteriaceae Subcommittee of the International Congress for Microbiology is made on the occasion of the Congress in Rome in 1953.

Although cultures 34, 732, 6108/50, and 606/51 are related to provisional *S. boydii* 10 cultures, it is thought advisable to refer to them as provisional *S. boydii* 11 rather than to place them under the provisional *S. boydii* 10 designation. Besides the fact that the two serotypes contain a specific antigen, it seems inadvisable to place both indol negative and indol positive strains within the same type designation.

Although these new *Shigella* types do not appear to be common, they have been found in widely separated parts of the world. The cultures mentioned above originated in Madagascar, North Africa, Italy, Mexico, and South or Central America. Szturm-Rugebensten (*13*) reports that three cultures which resemble D15 and D21 (provisional *S. boydii* 10) recently were isolated in Hanoi, Indochina. It seems probable that the new types will be recognized in other parts of the world as well.

Summary

Two additional *Shigella* serotypes are described. These are provisional *Shigella boydii* 10 (Szturm et al. *12*) and provisional *S. boydii* 11. The two serotypes are related but each contains a specific antigen. Cultures of provisional *S. boydii* 10 do not produce indol while provisional *S. boydii* 11 cultures do form this substance.

The heat-stable somatic antigens of provisional *S. boydii* 10 are related to those of *Escherichia coli* O group 105 but are not identical with them. The O antigens of provisional *S. boydii* 11 cultures are identical with those of *E. coli* 0105 as demonstrated by reciprocal absorption tests.

Addendum

After this paper was submitted for publication, the three Hanoi cultures, mentioned in the discussion, were received from S. Szturm. All three are provisional *Shigella boydii* 11 cultures. S. Szturm informs us that the Hanoi cultures were grouped with D15 (provisional *Shigella boydii* 10) in a paper presented at the June 1951 meeting of the Societé francaise de Microbiologie.

Additional cultures of both provisional *S. boydii* 10 and 11 were isolated in Belgian Congo by Dr. Vandepitte, and Roja Sapiro has isolated cultures of provisional *S. boydii* 10 at Haifa.

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Incidence of Disease

No health department, State or local, can effectively prevent or control disease without knowledge of when, where, and under what conditions cases are occurring

UNITED STATES

Reports From States for Week Ended, September 22, 1951

Poliomyelitis

The total reported cases of poliomyelitis in the Nation was 1,746 for the current week, compared with 1,797 for last week. Since the seasonal low week for the current year, a cumulative total of 17,889 cases has been reported, compared with 18,407 for the corresponding period in 1950. The cumulative total for the calendar year is 19,101, compared with 19,538 for the 1950 calendar year.

Of the nine geographic divisions, six decreased from the preceding week and three increased for the same period. The East North Central increased from 447 last week to 486 for the current week; the East South Central, from 110 to 154; and the Pacific, from 194 to 219.

Wisconsin reported that cases of poliomyelitis increased from 100 last week to 151 for the current week. Other States reporting more than 100 cases for the week were: California 172, New York 121, and Illinois 116.

States reporting the largest decreases were: Colorado, from 67 to 41; Missouri, from 79 to 55; and Utah, from 49 to 26.

A summary of the 241 cases of poliomyelitis reported in Arkansas between January 1 and September 1 shows that 130, or 54 percent, occurred in 3 counties. These cases were distributed by age as follows: 109 were under 5 years, 52 were 5 to 9, 32 were 10 to 14, and 48 were 15 years of age and over. There have been 10 deaths. The proportion of cases in the older age group, 19.9 percent, is more than twice that for 1949 when 9.3 percent were 15 years of age and over.

Malaria

For the current week, 57 cases of malaria in civilians and 208 cases in the military were reported. The largest civilian totals were reported in Georgia, 16, and Wisconsin, 23. The largest military totals were reported in Maryland, 20, Massachusetts, 28, Pennsylvania, 25, South Carolina, 47, and Texas, 21.

Epidemiological Reports

Erythema Contagiosum

Dr. C. C. Kuehn, Louisiana Department of Health, reports the occurrence of several cases of a disease entity resembling erythema contagiosum in and around Baton Rouge. Children 3 to 6 years of age are principally affected.

Keratoconjunctivitis

Dr. A. A. Jenkins, Utah Department of Health, has reported an outbreak of keratoconjunctivitis occurring mainly in a school for Indians located in Box Elder County. An ophthalmologist stated that a few cases were seen in the spring of 1951, but the outbreak, explosive in character, started during the last week of August and continued into September. It is now subsiding. A total of 750 cases has been reported from the school. Bilateral nonpurulent conjunctivitis was observed in most cases, and enlargement of preauricular lymph nodes was seen in a few instances. Acute and convalescent phase blood serum specimens are being studied.

Gastroenteritis

Dr. R. F. Feemster, Massachusetts Department of Health, has reported five cases of food poisoning in persons eating baked ham sandwiches in a local restaurant on September 4. All become violently ill with vomiting, diarrhea, and chills 3 to 4 hours after eating the ham.

Comparative Data for Cases of Specified Reportable Diseases: United States

[Numbers after diseases are International List numbers, 1948 revision]

Disease	Total for week ended—		5-year median 1946–50	Seasonal low week	Cumulative total since seasonal low week		5-year median 1945–46 through 1949–50	Cumulative total for calendar year—		5-year median 1946–50
	Sept. 22, 1951	Sept. 23, 1950			1950–51	1949–50		1951	1950	
Anthrax (062)		2		(1)	(1)	(1)	(1)	46	32	40
Diphtheria (055)	101	136	186	27th	613	890	1,540	2,621	4,018	6,150
Encephalitis, acute infectious (082)	22	24	23	(1)	(1)	(1)	(1)	766	679	480
Influenza (480–483)	307	548	528	30th	2,289	2,939	2,825	118,344	141,703	131,027
Measles (085)	815	534	539	35th	2,561	1,858	1,649	471,472	289,729	553,666
Meningitis, meningococcal (057.0)	50	51	48	37th	50	51	48	3,111	2,850	2,686
Pneumonia (490–493)	413	674	(2)	(1)	(1)	(1)	(1)	48,261	64,167	(3)
Poliomyelitis, acute (080)	1,746	2,169	1,606	11th	[3]17,889	18,407	17,296	[3]19,101	19,538	17,646
Rocky Mountain spotted fever (104)	6	14	11	(1)	(1)	(1)	(1)	289	420	495
Scarlet fever (050)[4]	390	456	482	32d	1,694	1,857	2,357	55,080	42,027	59,446
Smallpox (084)			1	35th			2	11	26	51
Tularemia (059)	12	13	17	(1)	(1)	(1)	(1)	506	721	748
Typhoid and paratyphoid fever (040, 041)[5]	96	82	104	11th	1,826	2,078	2,364	2,261	2,588	2,849
Whooping cough (056)	1,082	1,792	1,792	39th	[6]74,390	117,101	100,165	[6]52,788	95,565	74,147

[1] Not computed. [2] Data not available. [3] Addition: Iowa, 22 cases, delayed report—not allocated. [4] Including cases reported as streptococcal sore throat. [5] Including cases reported as salmonellosis. [6] Addition: Utah, week ended September 15, 3 cases.

The ham was baked at the restaurant after being deboned. Specimens showed presence of *Staphylococcus aureus*.

Dr. D. S. Fleming, Minnesota Department of Health, reports 19 of 33 persons partaking of a picnic supper became ill 12 hours later with diarrhea. A nonhemolytic streptococcus found in hamburger and a barbecue sauce was the only evidence found in specimens of food.

Dr. R. M. Albrecht, New York State Department of Health, has reported two mild outbreaks of gastroenteritis in a camp in which unsatisfactorily chlorinated lake water was regarded as the source of infection. During periods of peak demand inadequate contact with chlorine was shown to exist. In another outbreak in a resort hotel, it was found that food handling practices were poor. Dishwashing was poorly performed, and refrigeration facilities were not properly used.

Dr. W. L. Halverson, California Department of Public Health, reports seven cases of food poisoning after a roast turkey dinner. The illness followed 8 to 15 hours after eating the turkey and dressing. The laboratory reported negative results of examination of the roast turkey, but hemolytic *Staphylococcus aureus* was found in the turkey dressing.

Reported Cases of Selected Communicable Diseases: United States, Week Ended Sept. 22, 1951

[Numbers under diseases are International List numbers, 1948 revision]

Area	Diphtheria (055)	Encephalitis, infectious (082)	Influenza (480–483)	Measles (085)	Meningitis, meningococcal (057.0)	Pneumonia (490–493)	Poliomyelitis (080)
United States	**101**	**22**	**307**	**815**	**50**	**413**	**1,746**
New England	**1**	**1**	**3**	**107**	**4**	**18**	**32**
Maine				27	1	5	2
New Hampshire			3	3		1	4
Vermont				11			2
Massachusetts	1	1		38	2		9
Rhode Island				8			1
Connecticut				20	1	12	14
Middle Atlantic	**6**	**4**	**2**	**184**	**12**	**53**	**226**
New York	5	2	(1)	110	9		121
New Jersey		2	2	46	1	18	41
Pennsylvania	1			28	2	35	64
East North Central	**6**	**2**		**185**	**6**	**53**	**486**
Ohio	3			34	2		89
Indiana	1			4		4	31
Illinois		1		54	2	31	116
Michigan	1	1		34	2	18	99
Wisconsin	1			59			151
West North Central	**4**	**3**	**3**	**38**	**3**	**20**	**238**
Minnesota			1	10	1	9	41
Iowa		2		1			34
Missouri	1	1	1	8			55
North Dakota				6		7	5
South Dakota	1			2			7
Nebraska	2			1			38
Kansas			1	10	2	4	58
South Atlantic	**41**		**103**	**68**	**7**	**46**	**77**
Delaware							
Maryland	1		1	29		9	4
District of Columbia	1			2		16	1
Virginia	5		79	7	2	8	20
West Virginia	2			9	1		9
North Carolina	17			9	3		11
South Carolina	10		4	1	1	5	4
Georgia	2		19	4		8	24
Florida	3			7			4
East South Central	**32**	**6**	**3**	**30**	**8**	**20**	**154**
Kentucky	6			9	1	4	12
Tennessee	14	2		3	2		59
Alabama	8	2		12	3	5	24
Mississippi	4	2	3	6	2	11	59
West South Central	**9**	**4**	**75**	**30**	**4**	**136**	**177**
Arkansas	1		50	2		23	24
Louisiana			5			23	47
Oklahoma	2		20	2	1	4	33
Texas	6	4		26	3	86	73
Mountain	**2**	**1**	**94**	**63**	**2**	**36**	**137**
Montana	2	1	10	32	2		28
Idaho				5			6
Wyoming				1			9
Colorado				4		11	41
New Mexico				8		9	8
Arizona			84	3		16	14
Utah				10			26
Nevada							5
Pacific		**1**	**24**	**110**	**4**	**31**	**219**
Washington			7	4			30
Oregon			9	18	1	13	17
California		1	8	88	3	18	172
Alaska							5
Hawaii				33			

[1] New York City only.

Reported Cases of Selected Communicable Diseases: United States, Week Ended Sept. 22, 1951—Continued

[Numbers under diseases are International List numbers, 1948 revision]

Area	Rocky Mountain spotted fever (104)	Scarlet fever [1] (050)	Smallpox (084)	Tularemia (059)	Typhoid and paratyphoid fever [2] (040, 041)	Whooping cough (056)	Rabies in animals
United States	**6**	**390**		**12**	**96**	**1,082**	**104**
New England		**24**			**5**	**93**	
Maine						7	
New Hampshire		2				7	
Vermont						2	
Massachusetts		17			5	56	
Rhode Island		2					
Connecticut		3				21	
Middle Atlantic	**1**	**55**			**6**	**195**	**18**
New York	1	21				107	10
New Jersey		2				34	
Pennsylvania		32			6	54	8
East North Central		**83**		**1**	**6**	**234**	**13**
Ohio		29			1	55	2
Indiana		6				11	6
Illinois		12		1	5	43	2
Michigan		22				71	3
Wisconsin		14				54	
West North Central		**27**			**7**	**52**	**14**
Minnesota		13				4	7
Iowa		6			2	7	2
Missouri		2			4	14	4
North Dakota						3	
South Dakota		1				1	
Nebraska						3	1
Kansas		5			1	20	
South Atlantic	**1**	**49**		**4**	**12**	**76**	**12**
Delaware							
Maryland	1	5		2		6	
District of Columbia		2				2	
Virginia		13		1	2	4	2
West Virginia		10			4	27	2
North Carolina		13		1	1	11	
South Carolina		3					5
Georgia		2			4	6	3
Florida		1			1	20	
East South Central	**2**	**45**		**2**	**14**	**55**	**19**
Kentucky		21			4	8	4
Tennessee	1	12			4	34	4
Alabama		9			3	4	5
Mississippi	1	3		2	3	9	6
West South Central	**1**	**15**		**3**	**12**	**239**	**26**
Arkansas	1	7		2	3	23	8
Louisiana		2			5	4	
Oklahoma		2			1	7	1
Texas		4		1	3	205	17
Mountain	**1**	**7**		**2**	**4**	**43**	**2**
Montana						3	
Idaho		1				3	
Wyoming		1		1		4	
Colorado		4			2	14	
New Mexico					2	2	2
Arizona						13	
Utah	1	1		1		4	
Nevada							
Pacific		**85**			**30**	**95**	
Washington		3				14	
Oregon		10			1	6	
California		72			29	75	
Alaska					1	1	
Hawaii		1					

[1] Including cases reported as streptococcal sore throat. [2] Including cases reported as salmonellosis.

FOREIGN REPORTS

CANADA

Reported Cases of Certain Diseases—Week Ended Sept. 8, 1951

Disease	Total	Newfoundland	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia
Brucellosis	11					4	6				1
Chickenpox	203			1		26	77	13	16	33	37
Diphtheria	5					4			1		
Dysentery:											
Amebic	1								1		
Bacillary	15					1	2				12
Encephalitis, infectious	1								1		
German measles	55			1		5	17		12	7	13
Influenza	17			17							
Measles	291	16		65	2	43	34	8	21	52	50
Meningitis, meningococcal	9			1		1		2	4		1
Mumps	208	2		1		11	96	17	36	14	31
Poliomyelitis	149			27	4	19	85	1	5	4	4
Scarlet fever	101			1		22	11	18	14	11	24
Tuberculosis (all forms)	163	6		1	9	61	17	11	6	31	21
Typhoid and paratyphoid fever	10					7	1			1	1
Venereal diseases:											
Gonorrhea	217	5		4	4	47	45	19	17	34	42
Syphilis	84	2		7	3	47	10	2	2	2	9
Primary	3					1	1		1		
Secondary	8					6				2	
Other	73	2		7	3	40	9	2	1		9
Whooping cough	211					50	96	8	13	28	16

REPORTS OF CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER RECEIVED DURING THE CURRENT WEEK

The following reports include only items of unusual incidence or of special interest and the occurrence of these diseases, except yellow fever, in localities which had not recently reported cases. All reports of yellow fever are published currently.

Cholera

Burma. For the week ended September 1, 1951, 176 cases (97 deaths) of cholera were reported in the country as a whole. During August and the first 2 weeks of September, 37 cases of cholera, 10 of which were for the week ended September 15, were reported in the seaport of Tavoy.

India. A sharp increase in the incidence of cholera was reported in two seaports for the week ended September 8, 1951, but for the following week a decrease was noted. The decrease was as follows: Madras, from 140 cases to 115, and Calcutta, 66 to 42.

Smallpox

Cameroons (French). During the period August 21–31, 9 cases of smallpox were reported as compared with 33 for the previous 10-day period.

Ceylon. The recent outbreak of smallpox has subsided with only 1 case being reported for the week ended September 15, 1951, as compared with 32 for the previous week.

Indochina. For the week ended September 8, 1951, 15 cases (3 deaths) of smallpox were reported in Cambodia.

Indonesia. Five cases of smallpox were reported in Bandoeng, Java, for the week ended September 1, 1951. For the previous week, two cases were reported. During the week ended September 1, four cases were reported in Balik Papan, Borneo.

Typhus Fever

Indochina. Typhus fever was reported in Viet Nam for the week ended September 15, 1951, as follows: Haiphong two cases and Saigon two.

Iran. During the week ended September 15, 1951, three cases of typhus fever were reported in Tabriz.

Yellow Fever

Colombia. During the period August 15–24, 1951, four fatal cases of jungle yellow fever were reported in the county of San Vicente de Chucuri, Santander Department.

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